Piperacillin/tazobactam versus imipenem/cilastatin for severe diabetic foot infections: a prospective, randomized clinical trial in a university hospital

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Abstract

In this prospective, randomized, open-label clinical trial, we compared the efficacy and safety of two antibiotic regimens for severe diabetic foot infections (DFI). Sixty-two in-patients with DFI received either piperacillin/tazobactam (Pip-Tazo, *n* = 30) (4.5 g intravenously every 8h) or imipenem/cilastatin (IMP, *n* = 32) (0.5 g intravenously every 6h). The mean duration of treatment was 21 days for Pip-Tazo and 24 days for IMP. Twenty-two (73.3%) patients in the Pip-Tazo group and 26 (81.2%) patients in the IMP group had DFI associated with osteomyelitis. Successful clinical response was seen in 14 (46.7%) patients in the Pip-Tazo group and in nine (28.1%) patients in the IMP group [relative risk (RR) 1.6 (95% CI 0.84–3.25), p 0.130]. Two patients in the IMP group and none in the PIP-Tazo group relapsed [RR 2 (0.94–4.24), p 0.058]. Eighty-nine microorganisms were isolated: 38 (43%) Gram-positive and 51(57%) Gram-negative. Among patients with positive culture, 47 (96%) had complete and two (4%) had partial microbiological response. Microbiological response rates were similar in both groups (p 1.000). Amputation was performed in 18 (60%) and 22 (69%) patients in the Pip-Tazo and IMP groups (p 0.739) respectively. Side effects were more common in the Pip-Tazo group (30% vs. 9.4%), but they were generally mild and reversible. In conclusion, although the sample size was small and the results did not reach statistical significance, Pip-Tazo produced a better clinical response rate than IMP in the treatment of severe DFI. There was no significant difference between the treatment groups with respect to microbiological response, relapse and amputation rates.

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Introduction

Diabetic wound infection is the most common cause of hospitalization in diatetic patients [1,2]. Severe diabetic foot infections (DFIs) lead to extremity amputations, reduced quality of life and mortality [3–7]. In addition to proper local wound care, DFIs require carefully selected antibiotic therapy. There are no specific recommendations for the choice of antibiotics in DFI [8]. Evidence-based reports and guidelines recommend that antibiotic therapy should be started empirically and include broad-spectrum cover [6,9]. Subsequent to empirical therapy, specific agents should be selected according to the results of culture and sensitivity tests and the patient's clinical response. Parenteral administration is usually preferred to achieve rapidly an adequate tissue concentration, particularly for moderate to severe DFI. Antibiotics such as ampicillin-sulbactam, piperacillin-tazobactam (Pip-Tazo), imipenem-cilastatin (IMP) or ertapenem are usually recommended for moderate to severe cases [3,4,6–11]. Although the efficacy of these agents is well-established in DFI, Pip-Tazo and IMP have not been compared head-to-head with each other before, particulary in patients with DFI associated with osteomyelitis.

In the present study, we compared the efficacy and safety profile of two parenteral antibiotic regimens, piperacillin-tazobactam (Pip-Tazo) and imipenem-cilastatin (IMP), for the treatment of moderate to severe DFI.

Materials and Methods

Study design and population

This was a prospective, single-centre, two-arm, randomized, open-label clinical trial, conducted in Cukurova University Hospital between April 2004 and August 2006.

Eligible patients were hospitalized adults (age ≥18 years) with a clinical diagnosis of moderate to severe diabetic lower extremity infection (Wagner grade 2–4) caused by bacteria known or suspected to be susceptible to Pip-Tazo or IMP. Exclusion criteria were treatment with any potentially effective antibiotic within the previous 48 h, hypersensitivity to any of the study medications, epilepsy, psychiatric illness, and pregnancy or lactation. All eligible patients were included in the study during a 2-year study period.

We used a random-number table prepared by Statistics Department of Cukurova University to allocate the patients to Pip-Tazo or IMP treatment arms. This table was kept by the AD Infectious Diseases Department of Cukurova University and study personnel called the AD to allocate recruited patients to study groups.

The study was approved by the Institutional Review Board of Cukurova University Medical School (Local Ethics Committee). All study participants provided their written informed consent before any study-related procedure. The trial was not registered.

Study procedures

Medical history and physical examination findings of the foot and other systems were recorded. Lesions were assessed for purulent discharge, erythema, fluctuation, warmth, pain or tenderness, induration, depth of wound and degree of soft tissue and bone involvement. The presence and extent of osteomyelitis were documented. Samples from skin biopsy, purulent secretions, debrided tissue or fine needle aspiration were cultured. In cases where a surgical intervention was required, deep tissue or bone biopsy material were cultured. Superficial wound swabs were not processed.

Optimal wound care was given by an experienced nurse, who was a member of the study group. Vacuum assisted closure was applied when necessary.

Patients were followed with hematological, biochemical, erythrocyte sedimentation rate and C-reactive protein values on days 1, 7, 14 and 28 of treatment. To determine microbiological response to therapy, follow-up cultures were obtained on days 4–7 and at the end of therapy when feasible.

All patients were followed for 2 months after discharge.

Study treatment

Eligible patients were randomized to receive one of the two drugs [Pip-Tazo (Tazocin®; Wyeth, Istanbul, Turkey) 3×4.5 g/day intravenously or IMP (Tienam®; Merck, Istanbul, Turkey) 4×500 mg/day intravenously]. Treatment was planned for 14 days. For osteomyelitis, treatment was administered for 28 days, counting from the time of debridment if performed. However, after total excision of infected bone, 5 days of treatment were considered adequate depending on the clinical response.

The antibiotic regimen was modified according to culture and susceptibility results. In cases with resistant *Enterococci* or methicillin-resistant *Staphylococcus aureus* (MRSA) glycopeptides were added to the therapy.

Study end-points

The primary end-point was the clinical response to the antibiotics tested. The complete regression of symptoms and signs such as purulent discharge, erythema or induration that were present before the treatment was recorded as 'cure' or 'response', whereas the persistence or progression of such findings was recorded as 'failure'.

Secondary end-points included relapse rate at the end of the 2 months follow-up. Patients who responded at first but whose symptoms and signs recurred after the completion of treatment were categorized as 'relapse'. A complete vs. partial eradication of microorganisms present before treatment was recorded as a 'complete' vs. 'partial' microbiological response, respectively.

Statistical analysis

SPSS 14.0 was used for the statistical analysis (SPSS Inc., Chicago, IL, USA). For comparison of variables, parametric or nonparametric tests were used, depending on the type and distribution of data. $p < 0.05$ was considered statistically significant.

Results

Demographic and clinical findings

Sixty-eight patients were eligible for the study. Four patients refused to participate in the study; 64 patients were randomized (31 to Pip-Tazo and 33 to IMP). Within 1 week of randomization, two patients (one in each group) were excluded as a result of an allergic reaction. The remaining 62 patients (39 male, 23 female) completed the study (Fig. 1).

Demographic and clinical characteristics of the patients are summarized in Table 1. Study groups were comparable

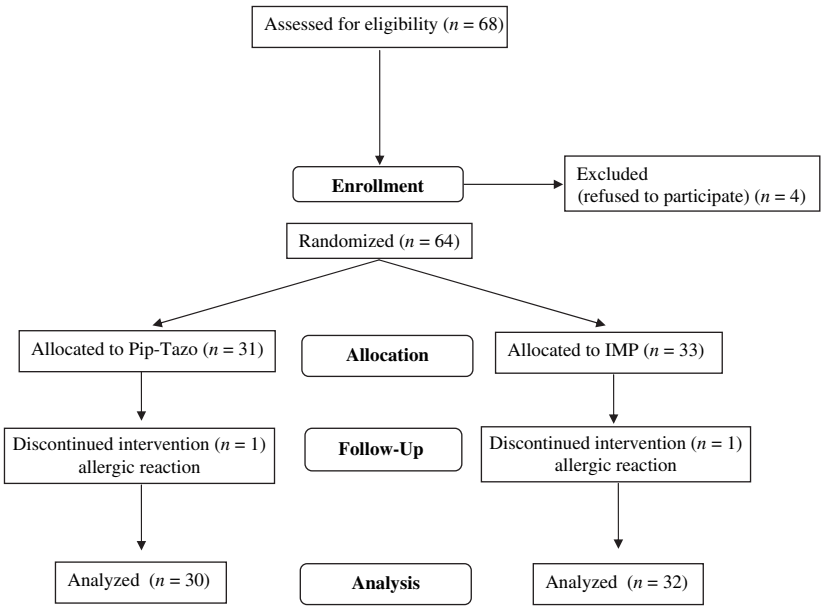

FIG. 1 Trial flow-diagram.

TABLE 1. Demographic and clinical characteristics of patients

	Pip-Tazo (*n* = 30)	IMP (*n* = 32)	p value
Age (median, range) (years)	58.3 (47–72)	58.5 (37–80)	0.942
Sex (*n*, %)			
Female	11 (36.7)	12 (37.5)	0.945
Male	19 (63.3)	20 (62.5)	
Co-morbidity (*n*, %)	20 (66.7)	22 (68.8)	0.810
Duration of diabetes (median, range) (years)	13.5 (3–30)	10.5 (0–30)	0.063
Prior antibiotic usage (median, range) (days)	21 (14–42)	24 (14–45)	0.431
Prior hospitalization (*n*, %)	15 (50)	10 (31.3)	0.213
Anti-diabetic usage before hospitalization (*n*, %)			
Oral anti-diabetics	14 (46.7)	18 (56.3)	0.300
Insulin	16 (53.3)	12 (37.5)	
Wagner class (*n*, %)			
Class 2	5 (16.7)	4 (12.5)	0.751
Class 3	15 (50)	19 (59.4)	
Class 4	10 (33.3)	9 (28.1)	
Width of ulcer (median, range) (mm)	32.5 (20–50)	30 (5–50)	0.847
Depth of ulcer (median, range) (mm)	25 (15–35)	20 (2–35)	0.103
Duration of infection (median, range) (days)	30 (7–50)	40.5 (3–120)	0.693
Ulcer duration before therapy (median, range) (days)	40.5 (3–120)	30 (7–150)	0.926
Type of infection (*n*, %)			
Osteomyelitis	22 (73.3)	26 (81.2)	0.05
Deep soft-tissue infection/infected ulcer	8 (26.7)	6 (18.8)	
Presence of ischaemia	5 (16.7)	7 (21.8)	
Duration of therapy (median, range) (days)	21 (14–42)	24 (14–45)	0.431
Microbiologically documented infection (*n*, %)	24 (80)	25 (78.1)	1.000
VAC treatment (*n*, %)	3 (10)	4 (12.5)	1.000

Pip-Tazo, piperacillin/tazobactam; IMP, imipenem/cilastatin; VAC, vacuum assisted closure.

in terms of age, sex, duration of diabetes, size of ulcer, and other clinical findings. Twenty-two (73.3%) in the Pip-Tazo group and 26 (81.2%) in the IMP group had DFI with an associated osteomyelitis. The duration of infection before inclusion in the study was 30 (7–50) days and 40.5 (3–120) days in the Pip-Tazo and IMP groups, respectively. The infection was microbiologicaly documented in approximately 80% of patients in both groups. The mean duration of therapy was 21 (14–42) days for patients in the Pip-Tazo group and 24 (14–45) days for patients in the IMP group (p 0.431). For three patients with MRSA isolates (two in the Pip-Tazo and one in the IMPgroup), a glycopeptide was added to the treatment. Study treatment was not changed for any other patient.

Clinical and microbiological outcomes

A successful clinical response was seen in 14 (46.7%) patients in the Pip-Tazo group and in nine (28.1%) patients in the IMP group [relative risk (RR) 1.6 (95% CI 0.84–3.25), p 0.130] (Table 2).

TABLE 2. Clinical response, side effects, and surgical intervention in study groups

	Pip-Tazo (*n* = 30)	IMP (*n* = 32)	p value
Clinical response	14 (46.7)	9 (28.1)	0.130
Relapse	0/14	2/9 (2.2)	0.058
Microbiological response			
Complete response	23/24 (95.8[a])	24/25 (96[a])	1.000
Partial response	1/24 (4.2[a])	1/25 (4[a])	
Surgical intervention			
None	3 (10)	4 (12.5)	0.739
Debridement	5 (16.7)	4 (12.5)	
Ray resection	4 (13.3)	2 (6.3)	
Amputation	18 (60)	22 (68.8)	
Side effects			
Total	9 (30)[b]	3 (9.4)	0.055
Hepatotoxicity[c]	5 (16.7)	1 (3.1)	
Nephrotoxicity[d]	6 (20)	1 (3.1)	
Hematological side effects	2 (6.7)	–	
Other (nausea)	–	1 (3.1)	

Data are given as *n* (%).
Pip-Tazo, piperacillin/tazobactam; IMP, imipenem/cilastatin.
[a]Percentage of patients with positive culture.
[b]Because one or more patients had more than one side effect in Pip-Tazo group, the total number of patients with any side effect is smaller than the total number patients who had different events.
[c]Hepatotoxicity is defined as an increase in either (a) alanine transaminase level more than three times the upper limit of normal, (b) alkaline phophatase level more than twice the upper limit of normal, or (c) total bilirubin level more than twice the upper limit of normal when associated with increased alanine transaminase or alkaline phophatase.
[d]Nephrotoxicity is defined as an elevated level of serum creatinine over the upper limit of normal.

During 2 months follow-up, two patients in the IMP group and none in the PIP-Tazo group relapsed, excluding the patients who had amputation [RR 2 (0.94–4.24), p 0.058].

Twenty-four patients in the Pip-Tazo group and 25 patients in the IMP group had a positive culture. Among these, 47 (96%) had complete and two (4%) had partial microbiological response. Microbiological response rates were similar in the two groups (Table 2).

Surgical outcomes

Sixty-four percent of patients (40/62) had amputations, 47% of which were minor digital amputations. Amputations were transmetatarsal in 10%, tarsometatarsal (i.e. Chopart) in 20%, and below the knee in 22.5% of the patients. Amputation was performed in 30 patients for uncontrolled infection, and in ten patients for ischaemia or non-infectious reasons such as Chopart. Patients who had amputations despite appropriate therapy were recorded as 'failures'.The addition of vancomycin was not considered as 'failure'.

As shown in Table 2, there was no statistically significant difference in amputation rates between the Pip-Tazo and IMP groups (60% vs. 68.8%, p 0.739).

Isolated microorganisms

Eighty-nine pathogens were isolated; 43% were Gram-positive and 57% Gram-negative bacteria. No anaerobic bacteria were isolated as a result of inappropriate specimen collection. Infection was monomicrobial in 38.7% and polymicrobial in 40.3% of patients.

The microorganisms isolated are shown in Table 3.

Pseudomonas aeruginosa (29.4%) was the most common pathogen isolated from Wagner class 3 wounds, followed by coagulase negative *staphylococcus* (CNS) (23.5%) and *Escherichia coli* (14.7%). *Enterococcus faecalis* (21.1%) was the most common pathogen isolated from Wagner class 4 wounds followed by *Morganella morganii* (15.8%) and *Streptococcus* spp. (10.6%). The most common pathogens isolated from Wagner class 2 wounds were CNS (55.6%) followed by *Streptococcus* spp. (22.2%), and *S. aureus* (22%).

Side effects

Thirty percent (*n* = 9) of the patients in the Pip-Tazo group and 9.4% (*n* = 3) in the IMP group experienced side effects (p 0.055). One patient from each group experienced a severe allergic reaction that required treatment interruption. Side effects in the treatment groups are summarized in Table 2.

Discussion

In the present study, we compared two broad-spectrum antibiotic regimens, Pip-Tazo and IMP, for the treatment of DFI. The clinical response rate was higher among the patients who received Pip-Tazo than those who received IMP (RR

TABLE 3. Isolated microorganisms in the study groups

	Pip-Tazo (*n* = 30)	IMP (*n* = 32)	p value
Total Gram-positive	20(66.6)	18 (56.2)	0.400
Total Gram-negative	23 (76.6)	28 (87.5)	0.264
Susceptible Gram-positives	18/20 (90)	17/18(94.4)	0.607
Susceptible Gram-negatives	23/23 (100)	28/28 (100)	1.000
Streptococcus spp.	4 (13.3)	4 (12.5)	
Streptococcus aureus	1 (3.3)	4 (12.5)	0.305
CNS	11 (36.7)	4 (12.5)	0.053
Enterococcus spp.			
Enterococcus feacalis	3 (10)	3 (9.4)	0.736
Enterococcus avium	1 (3.3)	2 (6.3)	
Enterococcus feaceium	0 (0)	1(3.1)	
Escherichia coli	3 (10)	4 (12.5)	1.000
Pseudomonas aeruginosa	7 (23.3)	6 (18.8)	0.759
Acinetobacter baumanni	0 (0)	3 (9.4)	0.238
Morganella morganii	4 (13.3)	3 (9.4)	0.703
Proteus spp.	1 (3.3)	4 (12.5)	0.318
Klebsiella spp.	2 (6.7)	2 (6.2)	0.998
Enterobacter cloaca	2 (6.7)	2 (6.2)	1.000
Citrobacter freundii	2 (6.7)	0 (0)	0.230
Gram-negative nonfermentative bacilli	0 (0)	1 (3.1)	1.000
Other	2 (6.7)	3 (9.4)	0.789
No microorganism isolated	6 (20)	7 (21.9)	

Data are given as *n* (%).
Pip-Tazo, piperacillin/tazobactam; IMP, imipenem/cilastatin; CNS, coagulase negative *staphylococcus*.

1.6), but the 95%CI included inferiority and superiority (0.84–3.25). There was no significant difference between the treatment groups with regard to microbiological response, relapse and amputation rates. Side effects were more commonly seen with Pip-Tazo, although most of them were mild and reversible.

In previous reports, Pip-Tazo and IMP were often the first choice antibiotic in life- or extremity-threatening DFI [12]. In three trials comparing intravenous regimens, no particular regimen was found to be superior to another [13–15]. One study evaluating the effectiveness of Pip-Tazo in DFI reported a 97% (22/23) response rate [16]. In another study comparing Pip-Tazo and ertapenem in DFI, treatment success was similar with the two regimens [11]. In a multicentre trial comparing Pip-Tazo and ampicillin/sulbactam in moderate to severe diabetic foot ulcers, clinical efficacy rates (cure or improvement) were equivalent (81% vs. 83%) [17]. In the present study, efficacy rates for both Pip-Tazo and IMP (47% vs. 28%) were relatively low, which may have been a result of the higher rate of patients with osteomyelitis or severe disease.

Microbiological studies are important for antibiotic management in the treatment of DFI [10]. Severe, limb-threatening or chronic infections are almost always polymicrobial [4,5,18–20] and Gram-negative rods and anaerobic organisms are frequently isolated together with Gram-positive cocci [4,11,21]. In the present study, the rate of polymicrobial infection was 40%, whereas 38% of the infections were monobacterial. Gram-negative bacteria were the most common (57%) pathogens, which is similar to the findings reported in previous studies [11,19,20,22,23]. This high rate can be attributed to the fact that patients with advanced disease and prior hospitalization/antibiotic use are usually referred to our centre. *P. aeruginosa, E. coli, Enterococcus* spp., *Acinetobacter baumannii,* and *Klebsiella* spp. were the most common microorganisms isolated in patients with a history of prior antibiotic usage, which is in accordance with other published reports [24,25].

The duration of treatment in severe or extremity threatening infections is based on the severity of infection [6,15]. There are no well-accepted guidelines for treating DFI associated with osteomyelitis [6]. The duration of therapy was 28–45 days in our patients with osteomyelitis There was no difference in duration of therapy between the two groups. The daily cost of Pip-Tazo was approximately €186 whereas that of IMP was €224.

In the present study, side effects included nephrotoxicity, hepatotoxicity, leukopenia and thrombocytopenia. However, two patients (one in each group) were excluded from the study as a result of severe allergic reaction. The overall side effect rate was 30% in the Pip-Tazo group and 9.4% in the IMP group. Several previous studies have also reported higher rates of side effects with Pip-Tazo than IMP, which were mostly mild and reversible [11,13,16,20,26]. According to biochemical markers, the number of patients who had hepatotoxicity and/or nephrotoxicity was 11 in the Pip-Tazo group and two in the IMP group. However, because hepatotoxicty and nephrotoxity may be caused by diabetes, it is difficult to be sure of the significance of these results.

DFI is best managed by a dedicated team via appropriate consultations [3,27,28]. Patients with severe infections or ischaemia should be hospitalized and closely monitored [4,21] and this was carried out in the present study. Optimal wound care was given by an experienced nurse, who was a member of the study group.

As far as we know, this is the first study comparing Pip-Tazo and IMP head-to-head in a prospective and randomized setting in a population of moderate to severe DFI with osteomyelitis. The major limitations of the study were the relatively small sample size and the open-label design. The implication of the small sample size of the study is that, although we found a difference between the treatment regimens with an advantage to Pip-Tazo, the 95% CI for this difference includes both inferiority and superiority.

In conclusion, we found that that Pip-Tazo was superior to IMP in terms of the clinical response rate in the treatment of moderate to severe DFI, although this difference was not statistically significant. Further controlled-studies with a larger sample size are required to show whether Pip-Tazo has a significant advantage over IMP for the treatment of moderate to severe DFI.

Transparency Declaration

This study was not funded by any pharmaceutical company or other source including internal support or grants from non-commercial (e.g. academic or governmental) institutions. None of the authors has any relationship (commercial or otherwise) that may constitute a dual or conflicting interest of any nature related to the submitted manuscript.

References

1. Lavery LA, Armstrong DG, Wunderlich RP, Mohler MJ, Wendel CS, Lipsky BA. Risk factors for foot infections in individuals with diabetes. *Diabet Care* 2006; 29: 1288–1293.
2. Apelqvist J, Bakker K, van Houtum WH, Schaper NC, International Working Group on the Diabetic Foot (IWGDF) Editorial Board. Practical guidelines on the management and prevention of the

diabetic foot: based upon the International Consensus on the Diabetic Foot (2007) Prepared by the International Working Group on the Diabetic Foot. *Diabet Metab Res Rev* 2008; 24 (suppl 1): S181–S187.
3. Lipsky BA, Berendt AR, Deery HG *et al.* Diagnosis and treatment of diabetic foot infections. Guidelines for diabetic foot infections. *Clin Infect Dis* 2004; 39: 885–910.
4. Frykberg RG, Zgonis T, Armstrong DG *et al.* American college of foot and ankle surgeons. Diabetic foot disorders. A clinical practice guideline (2006 revision). *J Foot Ankle Surg* 2006; 45 (suppl 5): S1–S66.
5. Brem H, Sheehan P, Rosenberg HJ, Schneider JS, Boulton AJM. Evidence based protocol for diabetic foot ulcers. *Plast Reconstr Surg* 2006; 117 (suppl 7): 193–209.
6. Lipsky BA. Evidence-based antibiotic therapy of diabetic foot infections. *FEMS Immunol Med Microbiol* 1999; 26: 267–276.
7. Ramsey SD, Newton K, Blough D *et al.* Incidence, outcomes, and cost of foot ulcers in patients with diabetes. *Diabet Care* 1999; 22: 382–387.
8. Rao N, Lipsky BA. Optimising antimicrobial therapy in diabetic foot infections. *Drugs* 2007; 67: 195–214.
9. Nelson EA, O'Meara S, Golder S *et al.* Systematic review of antimicrobial treatments for diabetic foot ulcers. *Diabet Med* 2006; 23: 348–359.
10. Frykberg RG An evidence-based approach to diabetic foot infections. *Am J Surg* 2003; 186 (suppl 5A): 44S–54S; discussion 61S–64S.
11. Lipsky BA, Armstrong DG. Ertapenem versus piperacillin/tazobactam for diabetic foot infections. (SIDESTEP): prospective, randomised, controlled, double-blinded multicenter trial. *The Lancet* 2005; 366: 1695–1703.
12. Lipsky BA. A report from the international consensus on diagnosing and treating the infected diabetic foot. *Diabet Metab Res Rev* 2004; 20 (suppl 1): S68–S77.
13. Bouter KP, Visseren FLJ, Van Loenhout RMM, Bartelink AKM, Erkelens DW, Diepersloot RJA. Treatment of diabetic foot infection: an open randomised comparison of imipenem/cilastatin and piperacillin/clindamycin combination therapy. *Int J Antimicrobial Agents* 1996; 7: 143–147.
14. Erstad BL Jr, McIntyre KE Jr, Mills JL. Prospective, randomized comparison of ampicillin/sulbactam and cefoxitin for diabetic foot infections. *Vascular Surg* 1997; 31: 419–442.
15. Grayson ML, Gibbons GW, Habershaw GM *et al.* Use of ampicillin/sulbactam versus imipenem/cilastatin in the treatment of limb-threatining foot infections in diabetic patients. *Clin Infect Dis* 1994; 18: 683–693.
16. Zeillemaker AM, Veldkamp KE. Piperacillin/tazobactam therapy for diabetic foot infection. *Foot & Ankle Inter* 1998; 19: 169–172.
17. Harkless L, Boghossian J, Pollak R *et al.* An open-label, randomized study comparing efficacy and safety of intravenous piperacillin/tazobactam and ampicillin/sulbactam for infected diabetic foot ulcers. *Surg Infect (Larchmt)* 2005; 6: 27–40.
18. Ge Y, MacDonald D, Hait H, Lipsky BA. Microbiological profile of infected diabetic foot ulcers. *Diabetic Med* 2002; 19: 1032–1035.
19. Carvalho CB, Neto RM, Araqao LP, Oliveira MM, Noqueira MB, Forti AC. Diabetic foot infection. Bacteriologic analysis of 141 patients. *Arq Bras Endocrinol Metabol* 2004; 48: 398–405.
20. Citron DM, Goldstein EJ, Merriam CV, Lipsky BA, Abramson MA. Bacteriology of moderate-to-severe diabetic foot infections and *in vitro* activity of antimicrobial agents. *J Clin Microbiol* 2007; 45: 2819–2828.
21. Grayson ML. Diabetic foot infections. Antimicrobial therapy. *Infect Dis Clin North Am* 1995; 9: 143–161.
22. Gadepalli R, Dhawan B, Sreenivas V, Kapil A, Ammini AC, Chaudhry R. A clinico-microbiological study of diabetic foot ulcers in an Indian tertiary care hospital. *Diabetes Care* 2006; 29: 1727–1732.
23. Shankar EM, Mohan V, Premalatha G, Srinivasan RS, Usha AR. Bacterial etiology of diabetic foot infections in South India. *Eur J Intern Med* 2005; 16: 567–570.
24. Armstrong DG, Lipsky BA. Advances in the treatment of diabetic foot infections. *Diabet Tech & Therap* 2004; 6: 167–177.
25. Motta RN, Oliveira MM, Megahaes PS *et al.* Plasmid mediated extended spectrum beta lactamase producing strains of Enterobacteriacea isolated from diabetic foot infections in a Brasilian diabetic center. *Braz J Infect Dis* 2003; 7: 129–134.
26. Brodsky J, Schneidler C. Diabetic foot infections. *Orthopedic Clin North Am* 1991; 22: 473–489.
27. Caputo GM, Joshi N, Weitekamp MR. Foot infections in patients with diabetes. *Am Fam Physician* 1997; 56: 195–202.
28. Pinzur MS, Slovenkai MP, Trepman E, Shields NN, Diabetes Committee of American Orthopaedic Foot and Ankle Society. Guidelines for diabetic foot care: recommendations endorsed by the diabetes committee of the american orthopaedic foot and ankle society. *Foot Ankle Int* 2005; 26: 113–119.